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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/473,830	12/28/1999	JEFFREY M. LEIDEN	2844/53802	1518

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/473,830	LEIDEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11-22-04 and amendment filed 12-16-04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-30,32,33,35-40,43 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30,32,33,35-40,43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-22-04 has been entered.

Applicants' amendment filed 12-16-04 has been entered. Claims 24 and 43 have been amended. Claims 41, 42, 44, 46 and 47 have been canceled. Claims 24-30, 32, 33, 35-40, 43 and 45 are pending and under consideration.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 24, 32, 33, 40, 43 and 45 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hammond et al., 1998 (WO 98/50079).

Claims 24, 32, 33, 40, 43 and 45 directed a method for stable and efficient transformation of cardiomyocytes by introducing an AAV vector expressing an angiogenic protein, such as FGF and VEGF, into cardiomyocytes via infusing said AAV vector into a coronary artery or a coronary sinus of an animal in an amount of $1x10^5$ to $1x10^9$ IU/gm, $1x10^7$ IU/gm, or $1x10^6$ to $1x10^8$ IU/gm body weight.

Hammond teaches a method for treating patient with congestive heart failure by delivering an AAV vector expressing FGF or VEGF to said patient via direct intracoronary injection of said AAV vector into coronary artery in an amount of AAV virus of 10^6-10^{14} particles or 10^8-10^{12} particles (e.g. p. 68-71). If a patient's average body weight is 60 kg, i.e. 60000gm, the amount of AAV virus injected to each patient would be 17 to $1.7x10^9$ particles/gm or $1.7x10^3$ to $1.7x10^7$ particles/gm body weight. The range of the AAV virus administered in the present invention falls within the range of the AAV virus taught by Hammond. The claims are

amended to read on "stable and efficient transformation" of cardiomyocytes, however, the specification fails to clearly define the phrase "stable and efficient transduction". Stable and efficient transduction does not mean that the nucleotide sequence has to be integrated into the genome of the cells. Transient expression of the encoded gene in the cell is considered "stable and efficient transduction". Although the specification states that "[F]or this invention, stable and efficient transduction means that significant number of cardiomyocytes are transduced and are capable of expressing the protein for a prolonged period of time. Stable and efficient transduction occurs over a period of time and can actually be observed over time as an increase in the percentage of transduced cardiomyocytes, as continued expression of the transgene, or as continued observation of the therapeutic effect at a molecular, microscopic or macroscopic level", there is no clear boundary of how many cardiomyocytes is considered "significant number". The number of cardiomyocytes transduced by rAAV vector using the method as taught by Hammond would be considered "significant number" and the number of cardiomyocytes transduced by the rAAV vector is expected to increase then decrease after the introcoronary injection of the rAAV vector. If an increase in the percentage of transduced cardiomyocytes, as continued expression of the transgene, is not anticipated by Hammond, it would have been obvious for one of ordinary skill in the art because it is a natural tendency to have an increase in transduced cells over a period of time after the initial transduction process. Thus, claims 24, 32, 33, 40, 43 and 45 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hammond et al., 1998 (WO 98/50079).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 24-30 and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al., 1998 (WO 98/50079) in view of Podsakoff et al., 1999 (US Patent No. 5,858,351).

Claims 24-30 and 35-39 are directed a method for stable and efficient transformation of cardiomyocytes by introducing an AAV vector expressing an angiogenic protein, such as FGF and VEGF, into cardiomyocytes via infusing said AAV vector into a coronary artery or a coronary sinus of an animal in an amount of $1x10^5$ to $1x10^9$ IU/gm, $1x10^7$ IU/gm, or $1x10^6$ to $1x10^8$ IU/gm body weight. Claims 25-30 and 37-39 specify the percentage of cardiomyocytes being tranduced by the AAV virus and number of minutes the AAV virus IU is infused into coronary artery.

The teachings of Hammond is as discussed above under 35 U.S.C. 102(a)/103(a) rejection. Hammond does not specifically teach the percentage of cardiomyocytes being tranduced by the AAV virus and number of minutes the AAV virus IU is infused into coronary artery.

Podsakoff teaches injecting incremental doses of rAAV-LacZ into the left ventricular apex of the rat heart and shows that greater than 50% of cardiomyocytes are transduced in the region of injection at each time point examined and the beta-gal staining persist in cardiac muscle for at least two months following gene transfer (e.g. column 22, Example 7).

It would have been obvious for one of ordinary skill in the art at the time of the invention to evaluate the percentage of the cardiomyocytes being transduced and to have 10%, 40%, or 50% of cardiomyocytes being transduced by the AAV virus vector by adjusting the amount of the AAV virus injected because Podsakoff shows stable and efficient transduction of cardiomyocytes by rAAV vector, i.e. greater than 50% of transduced cardiomyocytes and at least two months of continued expression of beta-gal. It also would have been obvious for one of ordinary skill in the art at the time of the invention to inject AAV virus into coronary artery for about 2 minutes to 30 minutes, 5 minutes to 20 minutes, or about 15 minutes because the amount of AAV virus administered in the present invention is taught by Hammond and the time required to administer said amount of AAV virus depends on how many virus particles are administered per minute.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to provide sufficient AAV virus to the target cardiomyocytes in a patient so as

to obtain therapeutic effect for treating congestive heart failure as taught by Hammond with reasonable expectation of success.

Applicants cite page 8, lines 10-16, of the specification that defines the phrase "stable and efficient transduction" and argue that it is a hindsight reconstruction and Hammond does not teach or suggest delivering any rAAV vector for a sufficient time to achieve stable and efficient transduction (amendment, p. 4-6). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 102/103(a) and 103(a) rejections.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Hammond teaches a method for treating patient with congestive heart failure by delivering an AAV vector expressing FGF or VEGF to said patient via direct intracoronary injection of said AAV vector into coronary artery in an amount of AAV virus of 10^6-10^{14} particles or 10^8-10^{12} particles. Transient expression of the encoded gene in the cell is considered "stable and efficient transduction". Although the specification states that "[F]or this invention, stable and efficient transduction means that significant number of cardiomyocytes are transduced...", there is no clear boundary of how many cardiomyocytes is considered "significant number". The number of cardiomyocytes transduced by rAAV vector using the

method as taught by Hammond would be considered "significant number" and the number of cardiomyocytes transduced by the rAAV vector is expected to increase after the introcoronary injection of the rAAV vector. Further, Podsakoff shows stable and efficient transduction of cardiomyocytes by rAAV vector, i.e. greater than 50% of transduced cardiomyocytes and at least two months of continued expression of beta-gal, when incremental doses of rAAV-LacZ were injected into the left ventricular apex of the rat heart. In view of the teaching of Podsakoff, it would have been obvious for one of ordinary skill in the art that the method taught by Hammond would provide stable and efficient transduction of cardiomyocytes via different infusion time and at least 10%, 25%, 40%, or 50% of cardiomyocytes could be transduced depending on the amount of rAAV vector delivered.

Applicants argue that Hammond does not consider transient expression to be a problem in his system and does not suggest administering rAAV for a sufficient time to achieve stable and efficient transduction of cardiomyocytes with rAAV and on of ordinary skill would not expect significant number of cardiomyocytes about 10%, 25%, 40%, or 50% to be transduced (amendment, p. 7). This is not found persuasive because of the reasons set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER